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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NEGIN, RUSSELL SCOTT	

ART UNIT	PAPER NUMBER
1631	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/672,515	ADORJAN ET AL.	
	Examiner	Art Unit	
	RUSSELL S. NEGIN	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 13-52* is/are pending in the application.

4a) Of the above claim(s) *18-24,26-43 and 45-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13-17,25,and 48-50, and 52* is/are rejected.

7)☒ Claim(s) *44 and 51* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/21/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Comments

Applicants' amendments and request for reconsideration in the communication filed on 13 June 2008 are acknowledged and the amendments are entered.

Accordingly, claims 1-11 and 13-52 are pending in the instant Office action.

Claims 1-11, 13-17, 25, 44, and 48-52 are examined in the instant Office action.

Claims 18-24, 26-43, and 45-47 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 16 December 2005.

Withdrawn Objections/Rejections

The objections to claims 1 and 10 because of informalities are withdrawn in view of amendments filed to the instant set of claims on 13 June 2008.

The rejections of claims 13-17, 25, 44, and 51 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention are withdrawn in view of amendments filed to the instant application on 13 June 2008.

The rejections of claims 13-17 under 35 U.S.C. 103(a) as being unpatentable over Tornaletti et al. in view of Laird et al. in view of Gaasterland et al. and further in view of Curtis et al. [Annals in Human Genetics, volume 65, pages 95-107, 2001] are

withdrawn in view of arguments filed by applicant on pages 16-19 of the Remarks of 13 June 2008.

Information Disclosure Statement

The information disclosure statement filed on 21 July 2008 has been considered.

Claim Objections

Claims 44 and 51 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 44 and 51 are free of the prior art because the prior art does not teach or selecting a defined number of epigenetic features based on the ranking resulting from the machine learning classifiers and determining a critical threshold through cross validation of the classifier relating to epigenetic features.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following rejection is reiterated from the previous Office action:

35 U.S.C. 103 Rejection #1:

Claims 1, 2, 10-11, 48-50, and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tornaletti et al. [Oncogene, 1995, volume 10, pages 1493-1499] in view of Laird et al. [US PGPub 2004/0033490 published 19 February 2004] in view of Gaasterland et al. [Nature Genetics, March 2000, volume 24, pages 204-206].

Claim 1 is drawn to a method for selecting epigenetic features comprising the following the following ten steps:

--collecting and storing biological samples with mammalian genomic DNA;

--collecting and storing available phenotypic information about the biological samples so as to define a phenotypic data set;

--defining at least one phenotypic parameter of interest;

--dividing the biological samples into at least two disjunct phenotypic classes of interest using the defined phenotypic classes of interest;

--selecting pairs or pairs of unions of classes from the disjunct phenotypic classes of interest;

--defining, for each selected pair, an initial set of epigenetic features of interest;

--analyzing the defined epigenetic features of interest of the biological samples so as to generate an epigenetic feature data set for each pair;

--selecting relevant epigenetic features of interest and/or combinations of epigenetic features of interest of the defined epigenetic features of interest, the relevant epigenetic features of interest and/or combinations of epigenetic features and/or combinations of epigenetic features of interest being relevant for epigenetically-based prediction of each pair of classes or pair of unions for the at least two phenotypic classes of interest;

--performing epigenetically-based prediction of each pair of classes or pair of unions of classes using a machine learning classifier.

The article of Tornaletti et al., entitled, "Complete and tissue-independent methylation of CpG sites in the p53 gene: implications for mutations in human cancers," states in the first sentences of its abstract:

> CpG dinucleotides are the target of about one third of transition mutations found in human genetic diseases and tumors. Methylation at these sites is thought to be the cause of these genetic changes through spontaneous deamination of 5-methylcytosine.

Collection and isolation of human genomic DNA are described in the "Materials and Methods" section on pages 1497-1498 under "DNA and cell culture" and "DNA isolation, base-specific modification and cleavage." (i.e. step (a) of instant claim 1).

The phenotype selected in this study is the presence or absence of certain types of cancers (two disjunct phenotypic classes of interest). The biological samples are

divided into portions specific to each type of cancer phenotype examined. The caption to Figure 1 on Tornaletti et al. states on page 1495:

> Figure 1. Genomic sequencing and methylation analysis of the human p53 gene. The autoradiogram shows the analysis of exon 5, upper strand. Lanes 1-2: C+T- and C-specific Maxam-Gilbert sequencing reactions of unmethylated p53-PCR products; lanes 3-11: C-specific Maxam –Gilbert sequencing reactions of genomic DNA isolated from the following sources: FIB, human skin fibroblasts; KER, normal human epidermal keratinocytes; LUNG, normal human bronchial epithelial cells; MAM, human mammary epithelial cells; COL, normal colonic mucosa cells; BLO, human peripheral blood lymphocytes; HeLa, HeLa S3 cells; CEM, leukemia CEM cells; T-47D, human breast carcinoma cells.

Consequently, Figure 1 of Tornaletti et al. collects and stores phenotypic information about the samples (step (b) of claim 1), defines the phenotypic parameters (i.e. cancers of interest; step (c) of claim 1), divides the samples into at least two disjunct phenotypic classes of interest (step (d) of claim 1).

Figure 1 of Tornaletti et al. comprises pairs of classes of disjunct types of phenotypes (i.e. different pairs of cancer types; step (e) of claim 1).

Tornaletti et al. continues in column 2, lines 36-40, by stating:

> Five out of six p53 mutation hotspot codons contain CpG dinucleotides (165, 245, 248, 273, and 282) indicating methylation-driven deamination of 5-mC as a major source of G:C→A:T transition mutations at CpG dinucleotides.

Consequently, Tornaletti et al. teaches an initial set of methylations (i.e. epigenetic features of interest). Figure 1 of Tornaletti et al. analyses these epigenetic features of interest by showing gels indicating respective methylations at each CpG dinucleotide of interest (165, 245, 248, 273, and 282) for each pair of phenotypic classes of interest (steps (f) and (g) of claim 1).

However, Tornaletti et al. does not teach the step of predicting phenotypic classes of interest from epigenetic data sets (step (h) of claim 1) or defining new

epigenetic features of interest based on epigenetic features of interest (step (i) of claim 1). In addition, Tornaletti et al. does not use machine learning classifiers to aid in predicting phenotypic information from epigenetic properties (step (j) of claim 1).

The study of Laird et al. discloses prediction of esophageal adenocarcinoma from epigenetic features of interest.

Claim 1 of Laird et al. is drawn to making a prediction of the esophageal cancer based on the methylation state of the genomic CpG sequences of a given profile of the epigenetic features of interest (i.e. step (h) of instant claim 1). Claim 6 in Laird et al. is based on claim 1 of Laird et al. wherein a new set of epigenetic features of interest are disclosed based on the list in claim 1 of Laird et al. (step (i) of instant claim 1).

While Tornaletti et al. and Laird et al. in combination predict phenotypes based on epigenetics, both studies do not use machine learning classifiers to aid in the process (step (j) of claim 1).

The study of Gaasterland et al., entitled, "Making the most of microarray data," states in the abstract:

> The impact of microarray technology on biology will depend on computational methods of data analysis. A supervised computer-learning method using support vector machines predicts gene function from expression data—and shows promise.

Gaasterland et al. explain the purpose of using machine learning classifiers in the bottom three columns of page 204:

> Microarray assays can measure the transcriptional effects of changes in gene function under different conditions. They can reveal genes that characterize tissue type, developmental stage, or responses to environmental conditions or genetic modifications. Microarray assays will therefore become a general feature of experimental protocols in genetics and cell physiology. As array data burgeon, new questions arose: if we, as a research community, collect all array hybridization data on a central location, can we assign new genes of unknown function to known functional classes? Can we correlate gene expression with gene function? Can we find new

> classes of co-regulated genes? Can we extract complete gene regulatory networks from microarray gene expression data?
>
> Computation is our only hope.... Support vector machines (SVMs) a supervised computer-learning method, [is used] to train a 'classification machine' to recognize new genes that are similar in expression pattern to groups of genes that are similar in expression pattern to groups of genes known to be co-regulated.

Figure 1 on page 205 of Gaasterland et al. illustrates the process of machine classification with a threshold. The caption states:

> Fig 1. A support vector machine (SVM) is a computational entity that accepts positive and negative training examples of a topic to be learned. As is 'learns', it draws a hyper-plane [threshold] which maximally separates input data points into two classes, members (green) and non-members (red). Here, input data is shown in three-dimensions...

Consequently, Gaasterland et al. uses machine learning classifiers to better classify genes and expression patterns of genes.

Claim 2 further comprises repeating steps based on the new set of epigenetic features of interest defined in the ninth step.

Claims 1-7 of Laird et al. repeat the epigenetic prediction and analysis with various different sets of epigenetic features of interest.

Claim 3 is further limiting wherein the biological samples include cellular components which contain DNA. Figure 1 of Tornaletti et al. displays genomic sequencing of sources of DNA.

Claims 4 and 5 are further limiting wherein the sample can be taken from breast tissue. The last three lines of column 2 of page 1497 of Tornaletti et al. indicate human breast carcinoma genomic DNA tissue as being used.

Claim 6 is further limiting wherein the phenotypic parameter of interest is selected from a kind of tissue and gene expression. Claim 7 is further limiting wherein the epigenetic features of interest include cytosine methylation sites on DNA. Figure 1 of Tornaletti et al. illustrates gene expression and cytosine methylation from various tissue types.

Claim 8 is further limiting wherein there is preliminary knowledge about the correlation between epigenetic features of interest and their correlation with phenotypic parameters of interest. The introduction on page 1493 of Tornaletti et al. indicates prior art that shows a correlation between mutations in the DNA (i.e. cytosine methylations and disease).

Claim 9 is further limiting wherein an accuracy or significance is likely to decrease by exclusion of epigenetic feature data.

Eliminating a lane from Figure 1 of Tornaletti et al. (i.e. the first or second lanes), makes the process of determining how cytosine methylations of p53 DNA affect the phenotypic outcome of the presence of cancer qualitatively much more difficult. This process described is repeated iteratively for various types of tissue shown in Figure 1 of Tornaletti et al.

Claim 10 is further limiting wherein the fifth step of the first claim is performed as to select pairs of unions of classes from the at least two disjunct phenotypic classes of interest.

Figure 1 of Tornaletti et al. divides the phenotypes into disjunct types of cancer phenotypes. All of the methylation "hot-spots" from any two cancers of interest comprise a union of pairs of classes of interest.

Claim 11 is further limiting wherein a machine classifier is utilized for prediction. As described above, the study of Gaasterland et al. utilizes machine learning classifiers.

Claim 48 is further limiting wherein the iterations in claim 1 are performed until a defined number of epigenetic features of interest are selected. Claim 49 is further limiting wherein features of interest with a combination score greater than a defined threshold are selected.

Claims 1-7 of Laird et al. repeat the epigenetic prediction and analysis with various different sets of epigenetic features of interest. For example, claims 7 and 10 of Laird et al. narrow the original set of epigenetic features in claim 1 and select a specified number of epigenetic features of interest. Claim 10 of Laird et al. also specifies a certain threshold in methylation level to be met in order to qualify as a methylated gene.

Claim 50 is further limiting comprising determining an optimal number of epigenetic features of interest using a crossvalidation of a machine learning classifier on test subsets of epigenetic feature data. Claim 52 is further limiting comprising training the machine learning classifier. Figure 2 of Gaasterland et al. illustrates the training of the machine learning classifier. Figure 1 of Gaasterland et al. illustrates training as well, showing validation of separation of disjunct phenotypes.

It would have been obvious at the time of the instant invention for someone of ordinary skill in the art to modify the study of the relation of cytosine methylation to human cancer of Tornaletti et al. by use of the epigenetic prediction study of Laird et al. and by use of the machine classification study of Gaasterland et al. where the motivation would have been that while Tornaletti et al. separated phenotype classes of interest and defined sites on the p53 gene which when methylated result in human cancer, Laird et al. describes cancer detection solely from epigenetic features in a way that increases the efficiency and amount of information that governs the conditions in each sample characterization [see for example, paragraph [0015] of Laird et al.] Furthermore, Gaasterland et al. expands on using machine classifiers to more efficiently and computationally analyze microarrays with many different samples (see for example, pages 204-205 of Gaasterland et al.)

Response to arguments:

Applicant's arguments filed 13 June 2008 have been fully considered and they are not persuasive.

With regard to Tornaletti et al., applicant argues that the abstract of Tornaletti et al. teaches away from the claimed invention because the abstract of Tornaletti et al. teaches that the methylation patterns are "tissue independent" and do not depend on tissue specific methylations for specific types of tumors. Therefore applicants contest that the abstract of Tornaletti et al. teaches away from steps g through h of the instant claim 1. This argument is not persuasive because this citation from Tornaletti et al. was taken out of context. Tornaletti et al. also states the following in the abstract:

> Our results are not inconsistent with theories that mutations in tumors with high CpG rates, like colon cancer, are caused by specific deamination of 5 methylcytosine and mutations in tumors with a lack of CpG involvement reflect superimposed fingerprints from exogenous carcinogens. However, given the lack of tissue specificity of methylation, alternative explanations (e.g. targeting of methylated CpG sites by tissue selective carcinogens) should be considered to explain the high percentage of CpG mutations in some tumor types.

Furthermore, Tornaletti et al. continues in the last paragraph of the introduction on page 1494:

> In order to define the contribution of 5-mCF to the p53 mutational spectra, observed in human tumors, it is necessary to know the methylation pattern of the p53 gene in different tissues. An initial analysis of the methylation status of the CpG dinucleotides at codon positions 175, 273, and 282 in the p53 gene, which correspond to hotspots for C→T or G→A mutations, has shown that these codons are methylated in white blooded cells, sperm and urothelial DNA,… in addition, analysis of the methylation status of the CpG dinucleotide at codon 248, a very frequently mutated codon in human tumors, has shown that this codon is methylated in white blood cells, sperm, muscle and kidney DNA.

Consequently, while Tornaletti et al. does teach tissue independent CpG methylations, these methylations should be taken into context with external factors that may result in the methylation hotspots indicative of cancers. The instant claims, as recited in step g through h of instant claim 1, do not exclude such factors; specifically

the claim only recites that the epigenetic features of interest must "RELEVANT" for prediction. Consequently, the hot-spots in Tornaletti et al. are indicative of the appropriate types of cancer.

Applicant argues with regard to the combination of Tornaletti et al., Laird et al. and Gaasterland et al. that the combination of references amounts to inappropriate hindsight because there is no motivation or reasonable expectation of success in combining Gaasterland et al. with Tornaletti et al. and Laird et al.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re*

Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the suggestion to combine is described above and reiterated below:

> It would have been obvious at the time of the instant invention for someone of ordinary skill in the art to modify the study of the relation of cytosine methylation to human cancer of Tornaletti et al. by use of the epigenetic prediction study of Laird et al. by use of the machine classification study of Gaasterland et al. where the motivation would have been that while Tornaletti et al. separated phenotype classes of interest and defined sites on the p53 gene which when methylated result in human cancer, Laird et al. describes cancer detection solely from epigenetic features in a way that increases the efficiency and amount of information that governs the conditions in each sample characterization [see for example, paragraph [0015] of Laird et al.] Furthermore, Gaasterland et al. expands on using machine classifiers to more efficiently and computationally analyze microarrays with many different samples (see for example, pages 204-205 of Gaasterland et al.)

There would have been a reasonable expectation of success in combining Tornaletti et al. and Laird et al. with the SVM of Gaasterland et al. because the theoretical techniques of Gaasterland et al. are computational and are generally applicable to the epigenetic contexts of Tornaletti et al. and Laird et al.

The following rejection is newly applied in view of the IDS filed on 21 July 2008:

35 U.S.C. 103 Rejection #2:

Claims 13-14 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tornaletti et al. in view of Laird et al. in view of Gaasterland et al. as applied to claims 1-11, 48-50, and 52 above, and further in view of Soussi et al. [Human Mutation, 2000, volume 15, pages 105-113; on IDS of 21 July 2008].

Claim 13 is further limiting wherein after definition of a candidate epigenetic feature selection and feature criterion selection, the candidate sets of epigenetic features are ranked and the highest ranking epigenetic features are chosen.

Claim 14 is further limiting wherein a set of all subsets of epigenetic features of interest are chosen.

Claim 17 is further limiting with the additional limiting of performing the predictions of phenotypes based on epigenetic features of interest using PCA.

Tornaletti et al., Laird et al., and Gaasterland et al. make obvious the use of machine learning classifiers for the purpose of predicting phenotypic properties based on epigenetic parameters, as described above. Gaasterland et al. uses PCA in column 3 of page 205 as a method of analysis which is independent of prior analysis, reduced the data set with many variables to a smaller number of uncorrelated variables.

Tornaletti et al., Laird et al., and Gaasterland et al. do not teach ranking of epigenetic feature sets.

The article of Soussi et al. uses a p53 website to analyze p53 gene mutations in human cancer and form a link between epidemiology and carcinogenesis.

Specifically, Figure 1 of Soussi et al. ranks cancer in the world through cross-referencing the cancers to the percentage of p53 mutations. Lung cancer is selected at the top of the list with the most cancer and the highest percentage of p53 mutations. Additionally, when taken together all of the p53 mutations for all of the cancers shown in Figure 1 of Soussi et al. form set of all of the subsets of cancers studies. Consequently, the study of Soussi et al. ranks cancers.

It would have been obvious to someone of ordinary skilled in the art at the time of the instant invention to modify the DNA methylation studies and machine classification methods of Tornaletti et al., Laird et al., and Gaasterland et al. by use of the cancer

prediction and cancer ranking methods of Soussi et al. where the motivation would have been that using the database ranking and classification methods of Soussi et al. gives the user a better perspective on the relative significance of each relation between epigenetic feature sets (i.e. p53 mutations) and the occurrence of specific types of cancer (see, page 106 and Figure 1 of Soussi et al.)

The following rejection is newly applied:

35 U.S.C. 103 Rejection #3:

Claims 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tornaletti et al. in view of Laird et al. in view of Gaasterland et al. in view of Soussi et al. as applied to claims 1-11, 13-14, 17, 48-50, and 52 above, and further in view of Claverie [Human Molecular Genetics, 1999, volume 8, pages 1821-1832].

Claims 15 and 16 are further limiting wherein each epigenetic feature set is assigned a cardinality, the highest cardinality being chosen as the epigenetic features of interest.

Tornaletti et al., Laird et al., Gaasterland et al. and Soussi et al. make obvious the use of machine learning classifiers for the purpose of predicting phenotypic properties based on epigenetic parameters, as described above.

Tornaletti et al., Laird et al., Gaasterland et al. and Soussi et al. do not teach cardinality rankings in ranking epigenetic features of interest.

The article of Claverie teaches computational methods for the identification of differential and coordinated gene expression.

Specifically, column 2 on page 1825 of Claverie teaches rankings of the expression of genes relating to different experimental conditions using cardinality rankings.

It would have been obvious to someone of ordinary skilled in the art at the time of the instant invention to modify the DNA methylation studies and machine classification methods of Tornaletti et al., Laird et al., and Gaasterland et al. and the cancer prediction and cancer ranking methods of Soussi et al. by use of the cardinality rankings taught in Calverie because it is obvious to combine known elements in the prior art to yield a predictable result. In this instance, the cardinality rankings of Claverie are an alternate means of ranking genetic features. There would have been a reasonable expectation of success in combining Tornaletti et al., Laird et al., Gaasterland et al., and Claverie because the study of Claverie uses a general means of gene ranking applicable to the specific form study (and ranking) of epigenetic features as discussed in Tornaletti et al., Laird et al., Gaasterland et al., and Soussi et al.

The following rejection is newly applied in view of the IDS filed on 21 July 2008:

35 U.S.C. 103 Rejection #4:

Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tornaletti et al. in view of Laird et al. in view of Gaasterland et al. in view of Soussi et al. as applied to claims 1-11, 13-14, 17, 48-50, and 52 above, and further in view of Brown et al. [PNAS, 2000, volume 97, pages 262-267; on IDS of 21 July 2008].

Claim 25 is further limiting wherein the feature selection criterion includes a training error of the machine learning classifier trained on respective epigenetic feature data of the epigenetic feature data set corresponding to the candidate set of epigenetic features of interest and/or combinations of epigenetic features of interest.

Tornaletti et al., Laird et al., Gaasterland et al. and Soussi et al. make obvious the use of machine learning classifiers for the purpose of predicting phenotypic properties based on epigenetic parameters, as described above.

Tornaletti et al., Laird et al., Gaasterland et al. and Soussi et al. do not teach use of a training error as a criterion for epigenetic feature selection.

The article of Brown et al. studies knowledge based analysis of microarray gene expression data by using support vector machines.

Specifically, Table 1 of Brown et al. compares error rates for various classification methods.

It would have been obvious to someone of ordinary skilled in the art at the time of the instant invention to modify the DNA methylation studies and machine classification methods of Tornaletti et al., Laird et al., and Gaasterland et al. and the cancer prediction and cancer ranking methods of Soussi et al. by use of the classification error rates of Brown et al. wherein the motivation would have been that selecting the

classifier with the lowest error is most likely to result in the most accurate results (see Table 1 of Brown et al. and the discussion on page 264 of Brown et al.).

Conclusion

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, Ph.D., whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 7am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Marjorie Moran, Supervisory Patent Examiner, can be reached at (571) 272-0720.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only.

For more information on the PAIR system, contact the Electronic Business Center

(EBC) at 866-217-9197 (toll-free).

/RSN/
Russell S. Negin, Ph.D.
13 September 2008

/Marjorie Moran/
Supervisory Patent Examiner, Art Unit 1631